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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,594	06/22/2001	Vassilios Papadopoulos		6687

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/762,594	Applicant(s) PAPADOPOULOS ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16 and 41-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10-16,41 and 48-49* is/are allowable.

6)☒ Claim(s) *42-47 and 50-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10 July 2003 (Paper No. 17) has been entered in full. Claims 10-16 are amended and claims 1-9 and 17-40 are cancelled. Claims 41-76 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 10-16 and 41-76 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3-4 of the previous Office Action (Paper No. 16, 10 April 2003) are *withdrawn* in view of the amended specification, title, and submitted abstract abstract (Paper No. 17, 10 July 2003).

2. The objection to claims 3, 10, and 34-35 at pg 4 of the previous Office Action (Paper No. 16, 10 April 2003) is *withdrawn* in view of the cancelled claims (Paper No. 17, 10 July 2003). Please see Claim Objections, below.

3. The rejections to claims 1-5, 9-17, and 34-35 under 35 U.S.C. § 112, first paragraph paragraph (scope of enablement and written description), as set forth at pg 4-12 of the previous Office Action (Paper No. 12, 22 May 2001) are *withdrawn* in view of the amended and cancelled claims (Paper No. 17, 10 July 2003). Please see section on 35 U.S.C. § 112, first paragraph below.

4. The rejections to claims 1-5, 9-17, and 34-35 under 35 U.S.C. § 112, second paragraph (Paper No. 16, 10 April 2003) are *withdrawn* in view of the cancelled claims (Paper No. 17, 10 April 2003). Please see section on 35 U.S.C. § 112, second paragraph, below.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The basis for this objection is set forth at pg 3 of the previous Office Action (Paper No. 16, 10 April 2003). This objection is maintained and held in abeyance. However, Applicant is encouraged to submit a new oath or application data sheet at Applicant's earliest convenience.

Claim Objections

6. Claim 51 is objected to because of the following informalities: In line 2, the word "detectable" should be "detectably". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. Claims 42-47 and 53-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising a nucleotide sequence as set forth in SEQ ID NO: 2 or an isolated nucleotide sequence that comprises a nucleic acid sequence that encodes a fragment of the polypeptide as set forth in SEQ ID NO: 7, wherein the polypeptide fragment is capable of regulating progesterone biosynthesis, does not reasonably provide enablement for an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable of binding to a peripheral-type benzodiazepine receptor (PBR), that is capable of regulating steroid biosynthesis, or is capable of mediating cholesterol delivery. The specification is also not enabling for an isolated nucleic acid that encodes a polypeptide that is

capable of binding a PBR receptor, regulating steroid biosynthesis, or mediating cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 4-9 of the previous Office Action (Paper No. 16, 10 April 2003).

Applicant's arguments (Paper No. 17, 10 July 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification, at pg 12, lines 3-31, pg 40, lines 7-23, and Example 1 teaches how to identify polynucleotides that are at least 90% identical to the nucleic acids of claim 41 and that encode polypeptides that are capable of associating or bind with PBR using a yeast-based two-hybrid genetic assay. Applicant argues that the specification also teaches one of skill in the art how to identify variant polynucleotide sequences that hybridize under stringent conditions to the nucleic acid sequences of SEQ ID NO: 2 (pg 3-4, Example 3). Applicant contends that the variants recited in the new claims are also functionally defined and that the specification provides working examples that teach one of skill in the art how to screen for these functional requirements (see Example 1, Example 5).

Applicant's arguments have been fully considered but are not found to be persuasive. Although the specification may disclose general guidance as to what amino acid positions could potentially be altered (pg 3-4, Example 1, Example 5), the claims recite a large number of nucleic acid variants that encode the polypeptide of SEQ ID NO: 7. Undue experimentation would be required of the skilled artisan to generate the infinite number of variants recited in the

claims and screen the same for activity. Specifically, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions.

Relevant literature reports examples of growth factor polypeptide mutations which alter the normal activity of the polypeptide. For example, Wuyts et al. (J Immunol 163: 6155-6163, 1999) establishes that NH_2-and COOH- terminal truncations of granulocyte chemotactic protein-2 (GCP-2) have enhanced neutrophil chemotactic potency as compared to wild-type GCP-2 (abstract; pg 6157-6158). Sher et al. (J Biol Chem 274(49):35016-35022, 1999) disclose that keratinocyte growth factor (FGF-7) acts predominantly on cells of epithelial origin and regulates processes in embryonal and adult development, including cell growth, differentiation, cell migration, and repair of epithelial tissues (pg 35016, ¶ 1). Sher et al. demonstrate that point mutations in a loop of FGF-7 do not alter receptor binding affinity, but cause reduced mitogenic potency and reduced ability to induce receptor-mediated phosphorylation events (pg 35020-35021). Additionally, a SCF mutant called $Steel^{17H}$ (Sl^{17H}) induces melanocyte defects and sterility in males. The Sl^{17H} allele contains a mutation that results in the substitution of 36 amino acids in the SCF cytoplasmic domain with 28 novel amino acids (Kapur et al., Blood 94(6): 1915-1925, 1999). Kapur et al. teach that compound heterozygous Sl/Sl^{17H} mice manifest several hematopoietic abnormalities in vivo, such as red blood cell deficiency, bone marrow

hyperplasia, and defective thymopoiesis (pg 1917-1918; Figures 2-3). In vitro, both the soluble and membrane-associated Sl^{17H} isoforms exhibit reduced cell surface expression on stromal cells and diminished biological activity as compared to wild soluble and membrane-associated forms (abstract, pg 1919-1921; Figures 6-7). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, the specification fails to teach the skilled artisan how to use the make biologically active PAP7 variants without resorting to undue experimentation to determine what the specific biological activities of the variants are.

Furthermore, although the specification in the instant application teaches art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active PAP7 derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of variants as recited in the claims and to screen them for a desired activity. Such trial and error is considered undue.

The specification discloses that when DNA encoding a partial PAP7 sequence (192 amino acids of C-terminal sequence) is transfected into MA-10 cells, the PAP7 transfectants have significantly reduced levels of progesterone production as compared to control (pg 47, lines 12-26). The specification indicates that this result could indicate that the transfected PAP7 fragment is not fully functional and reduces the interaction between PBR and endogenous PAP7

(pg 51, lines 18-26). Therefore, the specification teaches that full length PAP7 increases progesterone biosynthesis while partial PAP7 decreases the level of progesterone biosynthesis. However, the specification does not teach any methods or working examples that indicate full length PAP7 or any PAP7 fragments are able to regulate the biosynthesis of steroids other than progesterone. The specification also does not teach any methods or working examples that indicate full length PAP7 or any PAP7 fragments are able to mediate cholesterol delivery.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which recite broad structural and functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 50-52 are directed to a diagnostic agent comprising a nucleic acid, wherein the nucleic acid is detectably labeled. The claims also recite a diagnostic agent comprising a single-

stranded nucleic acid, wherein the nucleic acid is complementary and is detectably labeled. The claims recite a diagnostic reagent comprising a single-stranded nucleic acid, wherein the nucleic acid amplifies PAP7 sequences.

The specification of the instant application teaches that the invention relates to a diagnostic kit for the detection of PAP RNA in cells (pg 26, lines 23-25). The specification also discloses that once PAP is detected, a determination whether the cell is overexpressing or underexpressing PAP can be made by comparison to the results obtained from a normal cell using the same method (pg 26, lines 14-17). The specification teaches that diagnostic methods can be predictive of diseases involving PBR including gallstones, atherosclerosis, multiple sclerosis, and tumorigenesis, among others (pg 30, lines 16-29). However, the specification does not disclose a correlation between a specific disease state and an alteration in expression level, form, temporal pattern, etc. of the PAP7 nucleic acid sequence of SEQ ID NO: 2. Significant further experimentation would be required of the skilled artisan to identify individuals with a disease involving the PAP7 nucleic acid molecule of SEQ ID NO: 2. (Note, this issue could be overcome by deleting the word "diagnostic" from the claims.)

Due to the large quantity of experimentation necessary to determine a correlation in a specific disease with the PAP7 nucleic acid sequence of SEQ ID NO: 2, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of identifying individuals with a disease involving PAP7, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 42-47 and 53-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 9-12 of the previous Office Action (Paper No. 16, 10 April 2003).

The claims are directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable of binding to a peripheral-type benzodiazepine receptor (PBR), that is capable of regulating steroid biosynthesis, or is capable of mediating cholesterol delivery. The specification is also not enabling for an isolated nucleic acid that encodes a polypeptide that is capable of binding a PBR receptor, regulating steroid biosynthesis, or mediating cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41.

Applicant's arguments (Paper No. 17, 10 July 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the structural and functional limitations of the subject matter of the new claims meet the Written Description Guidelines of the USPTO (February 2000). Applicant indicates that Example 14 of the Guidelines teaches that a claimed variant polynucleotide that has a high percent identity to a sequence taught in the specification, along with a functional limitation that the claimed variant polynucleotides encode variant polypeptides that exhibit a specified catalytic activity, meet the written description if the required activity can be determined as described in the specification. Applicant argues that biological activities of the polypeptides variants can be measured in assays described in Examples 1 and 5.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polynucleotides recited in the claims. The description of one full length PAP7 polynucleotide and polypeptide and one partial PAP7 polynucleotide and polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and variants with at least 90% or more sequence identity to the polypeptide of SEQ ID NO: 7. Therefore, only an isolated nucleic acid comprising the nucleotide sequence of SEQ ID NO: 2 and an isolated nucleic acid molecule which encodes a fragment of the polypeptide as set forth in SEQ ID NO: 7 that is capable of regulating progesterone biosynthesis, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Furthermore, the broad brush discussion of making or screening for variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

Furthermore, the fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the protein and variants have a specific activity disclosed in the specification. However, regarding the PAP7 polynucleotides and polypeptides of the instant invention, the specification does not teach any significance or functional characteristics of all possible PAP7 polynucleotide

sequences that are 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 or to the nucleotide sequence that encodes the polypeptide set forth in SEQ ID NO: 2.

Additionally, the recitation of hybridization conditions in the claims does not yield adequate written description of the polynucleotides encompassed. The claims encompasses an infinite number of polynucleotides that hybridize to the nucleic acid sequence of SEQ ID NO: 2. These polynucleotides may be structurally and functionally divergent from the polynucleotide of SEQ ID NO: 2.

35 USC § 112, second paragraph

10. Claims 45-47 and 65-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 45-47 and 65-76 are rejected as being indefinite because it is not clear how the isolated nucleic acids hybridize to the complement of the complement recited in claim 41(c). (Please note that this issue could be overcome by amending the claims to recite that the isolated nucleic acids hybridize to the complement of the nucleic acid of claim 41(a) or 41(b).)

Conclusion

Claims 10-16, 41, 48-52 are allowable. Claims 42-47 and 53-76 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
15 September 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER